REMARKS

Applicants gratefully acknowledge the March 10, 2005 interview granted by the Examiner with Applicants' representative Jonathan Hallman. The interview was carefully summarized by the Examiner in the 3/14/05 office action. Although agreement was not reached regarding the new matter issues, Applicants have mooted these issues by canceling the objected-to amendments made to the specification in the response of 4/20/04. Specifically, the paragraphs on page 1, line 19; page 2, line 13; page 4, line 17; and page 5, line 29 have been returned to their original form. Moreover, the two paragraphs that had been deleted starting at page 18, line 31 have been re-inserted. Finally, the paragraph on page 19, line 17 has been returned to its original form.

Applicants note that these paragraphs were clearly at variance with the remainder of the specification and thus should rightfully be correctable by the Applicants. However, because these paragraphs are merely describing embodiments of the invention, the claims are in no way limited by these erroneous paragraphs. Applicants thereby see no harm in re-inserting such erroneous paragraphs.

Claim 109 has been amended to address the informality noted in the 3/14/05 office action. Moreover, claim 109 has been amended to address the 35 USC 112, second paragraph issue in that the mass spectrometer is indeed under the control of the controller as clearly shown, for example, by Figure 2 and the accompanying description in the specification. In addition, the structural coupling between the elements has been made explicit (albeit already inherently present). For example, the spike dilution apparatus is coupled to the spike reservoir, the mixer is coupled to the spike dilution apparatus, and so on. Because claims 114, 115, 116, 117, 121, and 124 are cancelled, their rejections are mooted.

Claim 119 has been amended to remove the limitation "wherein the second concentration is selected based upon an estimate of a concentration of the analyte in a sample." Although Applicants note that they are allowed to broadly claim such that the objection "it is not clear what basis is used for the estimate: the concentration that should be in the solution analyzed, a guess, a previous measurement or a number that is entered in the control system" is non-statutory: the estimate may be those things or it may be

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something else: Applicants are allowed to claim as broadly as their specification and the prior art allows. Here, applicants have plainly disclosed that the dilution of the spike is based "in embodiments of the invention that the relative concentration of the spike for any specie for which monitoring is accomplished be in the same general range as the expected concentration in the sample." (emphasis added). Page 30, lines 22 – 25. However, to moot the issue, the "wherein" clause has been deleted from claim 119.

Having settled these ancillary issues, Applicants address the real issue: for the first time in the history of mass spectrometry, a closed loop in-process mass spectrometry system has been developed that allows the automated characterization of constituents and trace elements in solutions. By "closed loop," Applicants are referring to the fact that not only are samples automatically drawn and characterized in a mass spectrometer, a spike is also automatically diluted and mixed with the sample prior to processing through the mass spectrometer. Because the spike concentration is known (even after dilution), a ratio response may be used to automatically characterize the amount of an analyte in the sample. As disclosed by the Applicants, the spike may be one that alters an isotopic ratio (an IDMS spike) or it may be a chemical homologue spike – for example, as stated by the Applicants on page 35, the invention includes numerous other embodiments that do not use the IDMS technique. For example, as stated on lines 8 – 11 of that page: "in some cases addition of standard concentrations of monoisotopic elements, that is, elements that do not exhibit a plurality of isotopes in the natural state, may be used in many procedures." For this reason, Applicants noted that their apparatus may be used to analyze for concentrations of Co and Mn on page 21, lines 4 through 10, both of which are virtually monoisotopic such that IDMS techniques cannot be used: there is no naturally-occurring isotopic ratio to alter for such elements.

A ratio measurement not using IDMS would involve the well-known internal standard technique. In that technique, the sample is spiked with a known concentration of an internal standard that chemically behaves sufficiently similar to the analyte of interest in the sample such that by comparing the mass/charge response for the analyte to the mass/charge response for the internal standard, the concentration of the analyte may be determined.

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Regardless of the type of ratio being used, the beauty of this invention is that instrument drift and other inaccuracies are naturally cancelled by the ratio measurement. Furthermore, the use of atmospheric pressure ionization (API) preserves chemical species information as compared to traditional IDMS techniques involving the use of inductively coupled plasma. Unlike the relatively harsh ionization used in traditional inductively-coupled plasma mass spectrometers , API provides a more mild ionization that preserves species information. For example, should the species Cr(III) and Cr(VI) be ionized in an inductively-coupled plasma MS instrument, they are ionized into the same state, namely Cr(I). A MS cannot distinguish between a Cr(I) ion that was originally Cr(III) vs. a Cr(I) ion that was originally Cr(VI). So, the species information is destroyed. However, the relatively mild ionization provided by an API ionization process would not convert Cr(III) and Cr(VI) into the same ionic form. For example, suppose a sample contains CrF_3 and CrF_6. When subjected to API, such a sample will provide $(CrF_2)+$ ions and $(CrF_5)+$ ions, thereby preserving the Cr(III) and Cr(VI) species information.

Moreover, the implementation of an API ionization stage is only one feature of Applicants' invention. For example, consider the dilution module described with respect to Figure 6. As described, for example, beginning at page 30, line 19, this dilution module may be controlled to achieve a desired level of dilution selected based upon an expected concentration range of the analyte-being-characterized in the sample. As appreciated by those of ordinary skill in the art, if a mass spectrometer is being used to characterize the concentration of an analyte at the parts-per-trillion range (ppt), one would now want to use a spike having a concentration in the parts-per-trillion range (ppt). However, as noted by the Applicants, most spike solutions become unstable at concentrations of less than the ppm range. Applicants have thus cleverly provided an automated system that can, on-the-fly, dilute a relatively-concentrated-but-stable spike to the appropriate diluted concentration.

These advantageous features are reflected in claim 109. For example, claim 109 recites "a control system adapted to automatically configure the spike dilution apparatus, the mixer, the API, and the mass spectrometer such that the sample is automatically mixed with the processed spike, ionized, and processed by the mass spectrometer, the control system being further configured to use the ratio measured by the mass

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spectrometer to characterize the concentration of the at least one analyte in the extracted sample."

Applicants respectfully traverse the obviousness rejections of the pending claims-. The "base" references of these rejections will be discussed first, followed by the "in view of' references.

The Base References:

The Marchante-Gayon reference merely discloses the use of a manually-operated ICP-MS apparatus. Applicants readily admit such an apparatus is abundantly in the prior art. The sole "automation" disclosed by Marchante-Gayon is the use of a two-channel peristaltic pump to continuously pump Mo spike through a first channel and alternatively one of either the sample or a naturally-occurring stock solution of Mo through a second channel. The spike solution is manually diluted. There is thus no suggestion or teaching whatsoever for a spike dilution apparatus coupled to a spike reservoir as recited in claim 109. Moreover, there is no teaching or suggestion for the use of an atmospheric pressure ionizer (API). Finally, there is no teaching or suggestion for a control system "adapted to automatically configure the spike dilution apparatus, the mixer, the API, and the mass spectrometer such that the sample is automatically mixed with the processed spike, ionized, and processed by the mass spectrometer, the control system being further configured to use the ratio measured by the mass spectrometer to characterize the concentration of the at least one analyte in the extracted sample."

The Viczian reference adds nothing further: it too discloses the use of a manually-operated ICP-MS instrument. Viczian thus provides no teaching or suggestion for a single limitation of claim 109.

Finally, the Rottmann reference also discloses the use of a manually-operated ICP-MS apparatus. Applicants again readily admit such an apparatus is abundantly in the prior art. Moreover, Applicants note that the "on-line" characterization of the Rottmann apparatus is misleading in that the "on-line" feature merely refers to the premixed spike being continuously pumped to one leg of a tee mixer where it is mixed with HPLC effluent and then sent to the ICP-MS (see, e.g., Figure 1 of this reference). Such an "on-line" feature is a far cry from Applicants' fully-automated apparatus that may be run

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without the need for human intervention. Thus, the Rottmann reference provides no teaching or suggestion for a single limitation of claim 109.

The "in view of" references:

Applicants immediately note that the Koster reference (USP 6,730,517) is merely directed to the use of an MALDI-TOF mass spectrometer. As known in the art, the MALDI-TOF technique is qualitative, not quantitative. Thus, all the Koster mass spec does is provide an indication whether a given genotype is present or not (see, e.g., Col. 19, lines 35-41). In that regard, Koster makes absolutely no teaching or suggestion for the "spike dilution apparatus" apparatus of claim 109. Instead, as known in the MALDI-TOF arts, a sample is mixed with a matrix and then dried to prepare it for analysis (see, e.g., Col. 17, line 60 through Col. 18, line 44). Furthermore, Koster makes no teaching or suggestion for the advantageous API stage of claim 109. Finally, Koster makes no teaching or suggestion for the limitations of "a mass spectrometer coupled to the API and configurable to process the ions by ratio determination; and a control system adapted to automatically configure the spike dilution apparatus, the mixer, the API, and the mass spectrometer such that the sample is automatically mixed with the processed spike, ionized, and processed by the mass spectrometer, the control system being further configured to use the ratio measured by the mass spectrometer to characterize the concentration of the at least one analyte in the extracted sample." In sum, Koster is deficient on each and every limitation of claim 109. In particular, Applicants respectfully traverse the assertion that "it would have been obvious ... to automatically prepare the spike as taught by ... Koster." Koster teaches absolutely no such spike preparation because the MALDI-TOF technique does not use spikes.

The sole teaching of the Maxwell reference is an "automated spike preparation system." The abstract does not disclose that this spike preparation system is "configurable to dilute a spike from the spike reservoir having a first concentration to produce a processed spike having a diluted second concentration" as set forth for the spike dilution apparatus of claim 109. Instead, all that is disclosed for the Maxwell spike preparation system is that the spikes have "duplicate net wts." Evidently, from the brief description in this abstract, one can only surmise that the electronic balance is used in an automatic fashion to weigh out aliquots of a prepared spike solution. As such, the

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Maxwell spikes are not produced at an arbitrary diluted second concentration as follows from the functional limitation of "configurable to dilute a spike ... having a first concentration to produce a processed spike having a diluted second concentration" in claim 109. Maxwell is entirely silent regarding the remaining elements of claim 109. Thus, just like Koster, Maxwell is deficient with respect to every limitation of claim 109. In that regard, Applicants respectfully traverse the assertion that "it would have been obvious ... to automatically prepare the spike as taught by ... Maxwell" because Maxwell does not teach the spike dilution apparatus recited in claim 109.

The Multala reference merely discloses a mass spectrometry system in which samples from various points in a distillation column are fed continuously into a mass spectrometer. Because no spiking is performed or suggested, the Multala apparatus could never characterize the concentration of the at least one analyte as performed by the system recited in claim 109. Accordingly, Mutlala provides no teaching or suggestion for a single limitation of claim 109.

Finally, the Durealt reference merely discloses a "fluidic module" configured to dilute samples. It is entirely silent with respect to the disclosure of any mass spectrometry let alone the automated ICP-MS system recited in claim 109. Accordingly, the Durealt reference provides no teaching or suggestion for a single limitation of claim 109.

The Kingston references (USP 5,414,259 and WO 99/39198) merely disclose the use of manually-operated ICP-MS to perform speciated analyses. Although a speciated analysis is within the scope of claim 109, Applicants have no need for the physical separation taught in the Kingston references because of the use of API rather than ICP ionization. More fundamentally, the Kingston references disclose no automation whatsoever. Accordingly, the Kingston reference provides no teaching or suggestion for a single limitation of claim 109.

Applicants note that claim 109 is not simply claiming "an automated mass spectrometer." There are six separate limitations in claim 109, all of which must be considered in forming an obviousness rejection. Based upon the art of record, such a rejection can only be grounded in sheer hindsight. Accordingly, claim 109 and its dependent claims 110 – 113 and 118 are patentable over the art of record. Method

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claims 119 and its dependent claims 120, 122, and 123 are patentable over the art of record analogously as discussed with respect to claim 109.

CONCLUSION

For the foregoing reasons, Applicant respectfully submits that the pending claims are in condition for allowance.

If there are any questions regarding any aspect of the application, please call the undersigned at 949-752-7040.

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